

# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For Receiving Office use only

International Application No.

International Filing Date

Name of Receiving Office and "PCT International Application"

Applicant's or agent's file reference  
(if desired)(12 characters maximum)

OCR-842

### Box No. I TITLE OF INVENTION

Central Nervous System Axon Regeneration

### Box No. II APPLICANT

Name and address (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.

Yale University  
Office of Cooperative Research  
155 Whitney Avenue  
New Haven, CT 06520-8336  
United States of America

☐ This person is also inventor.

Telephone No. (203) 432-5446

Facsimile No. (203) 432-5449

Teleprinter No.

State (i.e. country) of nationality US

State (i.e. country) of residence US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States ☐ the United States of America only ☐ the States indicated in the Supplemental Box

### Box No. III FURTHER APPLICANT(S) AND OR (FURTHER) INVENTORS(S)

Name and address (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Strittmatter, Stephen M.  
26 Pleasant Valley Road  
Clinton, CT 06413  
United States of America

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality US

State (i.e. country) of residence US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

### Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicants before the competent International Authorities as: ☒ agent ☐ common representative

Name and address (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Krinsky, Mary M.  
88 Prospect Street  
New Haven, CT 06511-3797  
United States of America

Telephone No. (203) 773-7544

Facsimile No. (203) 772-0587

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent

## Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

## Regional Patent

- ☐ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☐ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

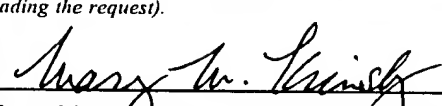
## National Patent (if other kind of protection or treatment desired, specify on dotted line):

- |   |   |
|---|---|
| <input type="checkbox"/> AL Albania                               | <input type="checkbox"/> LS Lesotho                                   |
| <input type="checkbox"/> AM Armenia                               | <input type="checkbox"/> LT Lithuania                                 |
| <input type="checkbox"/> AT Austria                               | <input type="checkbox"/> LU Luxembourg                                |
| <input checked="" type="checkbox"/> AU Australia                  | <input type="checkbox"/> LV Latvia                                    |
| <input type="checkbox"/> AZ Azerbaijan                            | <input type="checkbox"/> MD Republic of Moldova                       |
| <input type="checkbox"/> BA Bosnia and Herzegovina                | <input type="checkbox"/> MG Madagascar                                |
| <input type="checkbox"/> BB Barbados                              | <input type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input type="checkbox"/> BG Bulgaria                              |   |
| <input type="checkbox"/> BR Brazil                                | <input type="checkbox"/> MN Mongolia                                  |
| <input type="checkbox"/> BY Belarus                               | <input type="checkbox"/> MW Malawi                                    |
| <input checked="" type="checkbox"/> CA Canada                     | <input type="checkbox"/> MX Mexico                                    |
| <input type="checkbox"/> CH and LI Switzerland and Liechtenstein  | <input type="checkbox"/> NO Norway                                    |
| <input type="checkbox"/> CN China                                 | <input type="checkbox"/> NZ New Zealand                               |
| <input type="checkbox"/> CU Cuba                                  | <input type="checkbox"/> PL Poland                                    |
| <input type="checkbox"/> CZ Czech Republic                        | <input type="checkbox"/> PT Portugal                                  |
| <input type="checkbox"/> DE Germany                               | <input type="checkbox"/> RO Romania                                   |
| <input type="checkbox"/> DK Denmark                               | <input type="checkbox"/> RU Russian Federation                        |
| <input type="checkbox"/> EE Estonia                               | <input type="checkbox"/> SD Sudan                                     |
| <input type="checkbox"/> ES Spain                                 | <input type="checkbox"/> SE Sweden                                    |
| <input type="checkbox"/> FI Finland                               | <input type="checkbox"/> SG Singapore                                 |
| <input type="checkbox"/> GB United Kingdom                        | <input type="checkbox"/> SI Slovenia                                  |
| <input type="checkbox"/> GE Georgia                               | <input type="checkbox"/> SK Slovakia                                  |
| <input type="checkbox"/> GH Ghana                                 | <input type="checkbox"/> SL Sierra Leone                              |
| <input type="checkbox"/> GM Gambia                                | <input type="checkbox"/> TJ Tajikistan                                |
| <input type="checkbox"/> GW Guinea-Bissau                         | <input type="checkbox"/> TM Turkmenistan                              |
| <input type="checkbox"/> HR Croatia                               | <input type="checkbox"/> TR Turkey                                    |
| <input type="checkbox"/> HU Hungary                               | <input type="checkbox"/> TT Trinidad and Tobago                       |
| <input type="checkbox"/> ID Indonesia                             | <input type="checkbox"/> UA Ukraine                                   |
| <input type="checkbox"/> IL Israel                                | <input type="checkbox"/> UG Uganda                                    |
| <input type="checkbox"/> IS Iceland                               | <input checked="" type="checkbox"/> US United States of America       |
| <input checked="" type="checkbox"/> JP Japan                      |   |
| <input type="checkbox"/> KE Kenya                                 | <input type="checkbox"/> UZ Uzbekistan                                |
| <input type="checkbox"/> KG Kyrgyzstan                            | <input type="checkbox"/> VN Viet Nam                                  |
| <input type="checkbox"/> KP Democratic People's Republic of Korea | <input type="checkbox"/> YU Yugoslavia                                |
|   | <input type="checkbox"/> ZW Zimbabwe                                  |
| <input type="checkbox"/> KR Republic of Korea                     |   |
| <input type="checkbox"/> KZ Kazakhstan                            |   |
| <input type="checkbox"/> LC Saint Lucia                           |   |
| <input type="checkbox"/> LK Sri Lanka                             |   |
| <input type="checkbox"/> LR Liberia                               |   |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☐ . . . . .
- ☐ . . . . .

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

<b>Box No. VI PRIORITY CLAIM</b>		Further priority claims are indicated in the supplemental box <input type="checkbox"/>	
The priority of the following earlier application(s) is hereby claimed:			
Country (in which or for which the application as filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) <b>US</b>	<b>13 August 1997</b>	<b>60/055,268</b>	
Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the Receiving Office (a fee may be required).			
<input checked="" type="checkbox"/> The Receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) <b>1, US Serial No. 60/055,268</b>			
<b>Box No. VII INTERNATIONAL SEARCHING AUTHORITY</b>			
Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code made be used): <b>ISA/US</b>			
Earlier Search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested to base the international search, to the extent possible, on the results of that earlier search. identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:			
Country (or regional Office):	Date (day/month/year):	Number:	
<b>Box No. VIII CHECK LIST</b>			
This international application contains the following number of sheets: 1. request : 3 sheets 2. description : 27 sheets 3. claims : 3 sheets 4. abstract : 1 sheet 5. drawings : <u>11 sheets</u>  Total : 45 sheets		This international application is accompanied by the items marked below: 1. <input type="checkbox"/> separate signed power of attorney 2. <input type="checkbox"/> copy of general power of attorney 3. <input type="checkbox"/> statement explaining lack of signature 4. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 1* 5. <input checked="" type="checkbox"/> fee calculation sheet 6. <input type="checkbox"/> separate indications concerning deposited items 7. <input type="checkbox"/> nucleotide and/or amino acid sequence listing (diskette) 8. <input type="checkbox"/> other (specify):	
Figure No. <u>7</u> of the drawings (if any) should accompany the abstract when it is published.			
<b>Box No. IX SIGNATURE OF APPLICANT OR AGENT</b>			
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is now obvious from reading the request).			
 Mary M. Kinsky, Attorney for Applicants			

For Receiving Office use only

1. Date of actual receipt of the purported international application:  3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:  4. Date of timely receipt of the required corrections under PCT Article 11(2):  5. International Searching Authority specified by the applicant <b>ISA/</b>	2. Drawings  <input type="checkbox"/> received:  <input type="checkbox"/> not received:  6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid
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For International Bureau use only

Date of receipt of the record copy by the International Bureau	
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# PATENT COOPERATION TREATY

PCT

## NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

KRINSKY, Mary, M.  
88 Prospect Street  
New Haven, CT 06511-3797  
ÉTATS-UNIS D'AMÉRIQUE

**RECEIVED**  
**MAR 09 1999**

*h26*

Date of mailing (day/month/year) 25 February 1999 (25.02.99)		IMPORTANT NOTICE	
Applicant's or agent's file reference OCR-842			
International application No. PCT/US98/16794	International filing date (day/month/year) 12 August 1998 (12.08.98)	Priority date (day/month/year) 13 August 1997 (13.08.97)	
Applicant YALE UNIVERSITY et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:  
AU,EP,JP,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:  
CA

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 25 February 1999 (25.02.99) under No. WO 99/08533

### REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

### REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer  J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

# PATENT COOPERATION TREATY

**PCT**

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year)

10 May 1999 (10.05.99)

International application No.

PCT/US98/16794

Applicant's or agent's file reference

OCR-842

International filing date (day/month/year)

12 August 1998 (12.08.98)

Priority date (day/month/year)

13 August 1997 (13.08.97)

Applicant

STRITTMATTER, Stephen, M.

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

10 March 1999 (10.03.99)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Sean Taylor

Telephone No.: (41-22) 338.83.38

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 19 OCT 1999

WIPO PCT

Applicant's or agent's file reference OCR-842	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/16794	International filing date (day/month/year) 12 AUGUST 1998	Priority date (day/month/year) 13 AUGUST 1997
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant YALE UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  10 MARCH 1999	Date of completion of this report  27 SEPTEMBER 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  DAVE NGUYEN
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/16794

**I. Basis of the report**

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments):*

- ☒ the international application as originally filed.
- ☒ the description, pages 1-27 , as originally filed.  
pages NONE , filed with the demand.  
pages NONE , filed with the letter of \_\_\_\_\_  
pages \_\_\_\_\_ , filed with the letter of \_\_\_\_\_
- ☒ the claims, Nos. 1-20 , as originally filed.  
Nos. NONE , as amended under Article 19.  
Nos. NONE , filed with the demand.  
Nos. NONE , filed with the letter of \_\_\_\_\_  
Nos. \_\_\_\_\_ , filed with the letter of \_\_\_\_\_
- ☒ the drawings, sheets/~~fig~~ 1-11 , as originally filed.  
sheets/~~fig~~ NONE , filed with the demand.  
sheets/~~fig~~ NONE , filed with the letter of \_\_\_\_\_  
sheets/~~fig~~ \_\_\_\_\_ , filed with the letter of \_\_\_\_\_

2. The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/~~fig~~ NONE

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/16794

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>1-18</u>	YES
	Claims <u>19 and 20</u>	NO
Inventive Step (IS)	Claims <u>1-18</u>	YES
	Claims <u>19 and 20</u>	NO
Industrial Applicability (IA)	Claims <u>1-20</u>	YES
	Claims <u>NONE</u>	NO

**2. CITATIONS AND EXPLANATIONS**

Claims 19 and 20 lack novelty under PCT Article 33(2) as being anticipated by JALINK ET AL.

Claims 19 and 20 are directed to an *in vitro* screening method for assaying the activity of any compound in inhibiting rho expression. JALINK ET AL. teach a screening method comprising adding the bioactive phospholipid lysophosphatidic acid (LPA) or a thrombin-receptor-activating peptide (TRP) to serum-starved N1E-115 or NG108-15 neuronal cells. The addition of LPA or TRP cause rapid growth cone collapse, neurite retraction. In addition, JALINK ET AL. teach that a subsequent addition of the *Clostridium botulinum* C3 exoenzyme to the cells inactivates the Rho small GTP-binding protein, inhibits LPA- and TRP-induced force generation and subsequent shape changes. Absent evidence to the contrary, the screening method of JALINK ET AL. has all of the properties cited in the claims.

Claims 1-18 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest *in vivo* gene therapy methods for providing central nervous system axon growth in any patient and/or pharmaceutical compositions employed in the gene therapy methods.

Claims 1-20 meet the criteria set out in PCT Article 33(4) for industrial applicability.

----- NEW CITATIONS -----

NONE



**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention because:

Neither the description nor the prior art of record provides sufficient guidance and/or factual evidence for the skilled artisan to reasonable extrapolate from the *in vitro* neurite outgrowth in DRG neuronal cultures to the subject matter sought in the claims. In addition, it is not apparent how the *in vitro* environment of neurite outgrowth in neuronal cultures represents a therapeutic effect generated by an increase of axon growth in the central nervous system in any patient. Simple expression of a marker gene and the C3-expressing recombinant adenovirus in rat cerebral cortex is not the same as a therapeutic effect resulting from the increase of axon growth in the central nervous system of all patients including a human patient. The application indicates that the promotion of axon regeneration in the central nervous system *in vivo* generates a treatment effect in a variety of central nervous system disorders including acute or chronic spinal cord injury, traumatic brain injury, and white matter stroke (page 5 of the description). However, none of the treatment effect has been demonstrated by either sufficient guidance or factual evidence disclosed in the description.

Claims 1-18 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/16794

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**CLASSIFICATION:**

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(6): A01N 43/04, 63/00; C12N 15/64, 5/00; A61K 38/00 and US Cl.: 424/93.21; 435/91.4, 325; 514/2, 44

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

**RECEIVED**  
DEC 30 1998  
*file*

**PCT**

To: MARY M. KRINSKY  
88 PROSPECT STREET  
NEW HAVEN, CT 06511-3797

## NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing  
(day/month/year)

**23 DEC 1998**

Applicant's or agent's file reference  
OCR-842

**FOR FURTHER ACTION**    See paragraphs 1 and 4 below

International application No.  
PCT/US98/16794

International filing date  
(day/month/year)  
12 AUGUST 1998

Applicant  
YALE UNIVERSITY

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

*NO. Lawrence For*  
DAVE NGUYEN

Telephone No. (703) 308-0196

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference OCR-842	<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <b>FOR FURTHER ACTION</b> </div> <div style="width: 50%;">                     see Notification of Transmittal of International Search Report                      (Form PCT/ISA/220) as well as, where applicable, item 5 below.                 </div> </div>	
International application No. PCT/US98/16794	International filing date <i>(day/month/year)</i> 12 AUGUST 1998	(Earliest) Priority Date <i>(day/month/year)</i> 13 AUGUST 1997
Applicant YALE UNIVERSITY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (See Box I).
  
2. ☐ Unity of invention is lacking (See Box II).
  
3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 

☐ filed with the international application.  
☐ furnished by the applicant separately from the international application.  

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ transcribed by this Authority.
  
4. With regard to the title,
 

☒ the text is approved as submitted by the applicant.  
☐ the text has been established by this Authority to read as follows:
  
  
5. With regard to the abstract,
 

☒ the text is approved as submitted by the applicant.  
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
  
6. The figure of the drawings to be published with the abstract is:
 

Figure No. \_\_\_\_\_

☐  
☐  
☐

as suggested by the applicant.  
 because the applicant failed to suggest a figure.  
 because this figure better characterizes the invention.

☒ None of the figures.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/16794

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :A01N 63/00; C12N 15/64, 5/00; A61K 38/00; A01N 43/04  
US CL :424/93.21; 435/91.4, 325; 514/2, 44

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.21; 435/91.4, 325; 514/2, 44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
APS, CAS ONLINE, MEDLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NISHIKI ET AL. ADP-Ribosylation of the rho/rac Proteins induces growths inhibition, neurite outgrowth and Acetylcholine Esterase. in Cultured PC-12 Cells. Biochemical and Biophysical Research Communications. 28 February 1990, Vol. 167, No. 1, pages 265-272, especially pages 270 and 271.	1-20
A	LUO ET AL. Rho family small GTP-binding proteins in growth cone signalling. Current Opinion in Neurobiology. 1997, Vol. 7, pages 81-86, especially pages 83 and 84.	1-20
A	NIKOLIC ET AL. The p35/Cdk5 kinase is a neuron-specific Rac effector that inhibits Pak1 activity. Nature. 10 September 1998, Vol. 395, pages 194-198, especially page 195.	1-20




Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	*&* document member of the same patent family

Date of the actual completion of the international search 06 NOVEMBER 1998	Date of mailing of the international search report 23 DEC 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer  DAVE NGUYEN Telephone No. (703) 308-0196

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/16794

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	ZIPKIN ET AL. Role of a New Rho Family Member in Cell Migration and Axon Guidance in <i>C. elegans</i> . <i>Cell</i> . 05 September 1997, Vol. 90, pages 883-894, especially page 891.	1-20
Y	LUO ET AL. Distinct morphogenetic functions of similar small GTPases: <i>Drosophila</i> Drac1 is involved in axonal outgrowth and myoblast fusion. <i>Genes &amp; Development</i> . 1994, Vol. 8, pages 1787-1802, especially page 1799, column 1.	1-20
Y	JALINK ET AL. Inhibition of Lysophosphatidate- and thrombin-induced Neurite Retraction and Neuronal Cell Rounding by ADP Ribosylation of the Small GTP-binding Protein Rho. <i>The Journal of Cell Biology</i> . August 1994, Vol. 126, No. 3, pages 801-810, especially page 809.	1-20
Y	US 5,543,498 A (FISHMAN et al) 06 August 1996, columns 3-6, especially column 4.	1-20
A,P	US 5,672,344 A (KELLEY et al) 30 September 1997, column 5.	1-20
Y	US 5,645,829 A (SHOCKLEY et al) 08 July 1997, columns 6-18, especially columns 7-8.	1-20
Y,P	US 5,661,033 A (HO et al) 26 August 1997, columns 8-12, especially column 11.	1-20